ORIGINAL ARTICLE

Belatacept after kidney transplantation in adolescents: a retrospective study

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SUMMARY

Regardless of recipient age at kidney transplantation (KTx), patients are at greatest risk for graft loss in adolescence, partly due to nonadherence to an oral immunosuppressive regimen. Belatacept, a non-nephrotoxic, first-in-class immunosuppressant that inhibits costimulation of T cells requires intravenous application only every 4 weeks, potentially leading to better adherence. However, it is only approved for use in adults. We report here the findings of the first study of belatacept in adolescents, comprising all patients in our department switched to belatacept post-KTx. Six patients (median age 15.5 years) were switched after a median of 7.5 months (range 23 days to 12 years), treatment range 3–28 months (cumulative 83 months): Three patients switched early (<3 months after KTx) had increased estimated glomerular filtration rate (GFR); one patient switched 12 years post-KTx has stable GFR; two patients were switched following rapid decline of and with markedly impaired GFR, changing slope in one patient. One patient had one acute rejection. In addition of two patients who received belatacept for other conditions, the only relevant adverse event was neutropenia (after a cumulative 109 months). Belatacept as primary immunosuppression is an option in Epstein–Barr virus-seropositive nonadherent adolescents if administered sufficiently early before deterioration of graft function.

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Key words
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Introduction

Belatacept is a first-in-class immunosuppressive drug that inhibits costimulation of T cells [1]. In contrast to the commonly used calcineurin inhibitors (CNI), such as cyclosporine A or tacrolimus, belatacept is not nephrotoxic. Other proposed advantages of belatacept include a reduced cardiovascular burden by causing less or no hypertension, hyperlipidemia, or both. A distinct feature of belatacept for maintenance immunosuppression is the intravenous application route; after the initial loading doses, applications every 4 weeks are sufficient. A large trial in adult patients proved that belatacept-based immunosuppression leads to a significantly higher glomerular filtration rate (GFR), which is associated with better graft survival compared with standard-dose cyclosporine regimen [2].

Regardless of recipient age at kidney transplantation (KTx), patients are at greatest risk for graft loss in adolescence [3]. This is in part due to a difficult transition from childhood to adulthood and from pediatric to adult care, but mainly because of increased

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nonadherence caused by behavioral changes in adolescence [4]. In this context, belatacept, with its 4-week intravenous dosing schedule, appears to be a prudent choice for a maintenance immunosuppressive regimen in this cohort, securing adherence for a crucial part of treatment with the aim of reducing loss of graft function and prolonging graft survival.

Both, the US Food and Drug Administration and the European Medicines Agency, have, however, only approved belatacept for adults. This is the first report on the use of belatacept in nonadherent, adolescent KTx recipients.

Methods

In this study, we included all adolescent patients treated in the Department of Pediatric Nephrology at Hannover Medical School who were switched to a belatacept-based immunosuppression post-KTx because of nonadherence to their immunosuppressive regimen, which was associated with an increase in serum creatinine. For assessment of safety outcome, we also report on two patients who received belatacept for other reasons. Belatacept was administered intravenously at weekday mornings in the outpatient clinic with 10 mg/kg on days 1, 5 and 14 and in weeks 4, 8 and 12 after the switch, followed by 5 mg/kg every 4 weeks thereafter. At time of switch to belatacept, the calcineurin inhibitor (cyclosporine A $n = 5$, tacrolimus $n = 1$) was stopped and the antiproliferative drug (everolimus, sirolimus or mycophenolate mofetil) was continued.

Data collection included the following: recipient age, gender, underlying kidney disease, panel-reactive antibodies and human leukocyte antigen mismatches before transplantation, time between KTx and start of belatacept, immunosuppressive regimen from transplantation before switch, age at start of belatacept, Epstein-Barr virus immune status at time of switch, height and serum creatinine at regular visits and once patients had stabilized. In addition, all acute and chronic rejection events, including histopathology as well as all assessments of donor-specific antibodies, were documented.

GFR was estimated by the bedside Chronic Kidney Disease in Children formula incorporating patient height and serum creatinine [5]. We plotted the course of eGFR for each patient separately, including a locally weighted scatterplot smoothing.

Medication nonadherence was defined by a combination of different items: self-reported problems with medication adherence, insufficient request for prescriptions for immunosuppressants, continuous detection of very low or zero trough levels of immunosuppressants (trough levels of mycophenolic acid were not measured), severe rejections (BANFF IIa/b or humoral rejection) in graft biopsies, early development of donor-specific antibodies with high mean fluorescence intensity. We used R (version 3.3.1) for all analyses and graphs [6,7].

According to the Professional Code of the German Medical Association (article B.III. § 15.1), no approval of the ethics committee was needed for this kind of study. All patients and families were informed about the intended off-label use of belatacept and gave informed consent for treatment with belatacept as an "individueller Heilversuch" (off-label use) in accordance with German law. Therefore, treatment was paid for by public German Health Insurance.

Results

Characteristics of nonadherent patients who received belatacept

The six patients (two female, four male) who received belatacept because of nonadherence were a median 15.5 years (range 15–17 years) at start of belatacept therapy (Table 1). Time between last KTx and start of belatacept was between 23 days and 12 years (median 7.5 months). The patient cohort comprised three patients with early belatacept treatment, defined as time between last KTx and start of belatacept of less than 3 months (23 days, 11 and 12 weeks, respectively) and in three patients with late treatment, defined as time between last KTx and start of belatacept of more than 3 months (12 and 22 months, and 12 years, respectively). All patients received graft biopsies before start of belatacept. Results and time points are given in Table 2. Donor-specific antibodies could be detected in patients 1, 3, and 4 at a time of 36, 12, and 2 months after transplantation before start of belatacept (Table 3). In four of six patients, panel-reactive antibodies were negative at time of KTx. In patient 4 and 5, panel-reactive antibodies of 6% and 10% could be detected, respectively (Table 3). The number of human leukocyte antigen mismatches at time of KTx is also given in Table 3.

Belatacept was scheduled for patient 1 because of severe nonadherence during treatment after his first KTx with highly variable trough levels of the immunosuppressants. Therefore, belatacept therapy was scheduled as a replacement for cyclosporine A after hospital discharge and at the beginning of outpatient treatment 23 days after the second KTx.

Table 1. Patient characteristics.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at KTx (years)	17	3	13	16	15	15
Gender	Male	Male	Female	Male	Female	Male
Underlying kidney disease	Transplant failure (solitary dysplastic kidney)	Renal dysplasia	Nephronophthisis	Renal dysplasia	Transplant failure (Deny–Drash syndrome)	Reactive FSGS
EBV-EBNA-VCA-IgG	Positive	Positive	Positive	Positive immediately before start of belatacept, negative thereafter	Positive	Positive
Time between last KTx and start belatacept	23 days	12 years	1 year 10 months	12 weeks	11 weeks	12 months
Age at start belatacept (years)	17	15	15	16	15	16
eGFR at start belatacept (ml/min/per 1.73 m^2)	49	39	23	46	46	15
eGFR trend before start belatacept	Unsteady	Slow decline	Rapid decline	Unsteady	Slow decline	Rapid decline
Observed duration of treatment with belatacept (months)	3	28	13	22	13	4
Current status regarding belatacept	Ongoing, transferred to adult nephrologist	Ongoing, transferred to adult nephrologist	Stopped, terminal transplant failure and hemodialysis	Ongoing	Ongoing	Ongoing
Immunosuppressive treatment besides belatacept	MMF	Sirolimus	Everolimus	Prednisolone, everolimus	Prednisolone, everolimus	Prednisolone, everolimus

EBV-EBNA-VCA-IgG, Epstein-Barr virus-Epstein Barr nuclear antigen-virus capsid antigen-immunoglobulin G; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; KTx, kidney transplantation; MMF, mycophenolate mofetil.

Table 2. Graft biopsy results.

Patient	Time between graft biopsy and start of belatacept (months)	Biopsy findings
1	No biopsy after second KTx	
2	8	Borderline rejection, 5% IF/TA
3	1	Borderline rejection, glomerulitis, graft vasculopathy, 60% IF/TA, ATN, benign arteriosclerosis
4	0.5	Cellular rejection BANFF IIb, tubulitis, glomerulitis, capillaritis, 10% IF/TA, ATN
5	0.5	Cellular rejection BANFF IIa, ATN
6	6	Cellular rejection BANFF IIa, humoral rejection BANFF II, 5% IF/TA

All biopsies were performed before start of belatacept.

ATN, acute tubular necrosis; IF/TA, interstitial fibrosis/tubular atrophy; KTx, kidney transplantation.

Table 3. Immunology at time of transplantation and detection of novo donor-specific antibodies.

Patient	Mismatches (HLA-A, B, DR)	PRA (%)	DSA type	Peak MFI	Time of first DSA detection after KTx (months)
1	2-2-1	0	A1	9817	36
2	0-0-0	0	Negative		
3	0-1-1	0	DQ2	23 848	12
4	1-1-1	6 (DQ5)	DQ2	9072	2
5	0-2-1	10 (A29)	Negative		
6	2-0-1	0	Negative		

DSA, donor-specific antibodies, HLA, human leukocyte antigen, MFI, mean fluorescence intensity, PRA, panel reactive antibody.

Patient 2 received his first KTx at the age of 3 years. Immunosuppression started with cyclosporine A and prednisolone, but because of CNI nephrotoxicity, mycophenolate mofetil (MMF) was added 10 months after KTx in order to reduce the cyclosporine A dose. Prednisolone was discontinued 1 year after KTx. Five years after KTx immunosuppression was changed to sirolimus and mycophenolate sodium (MPS) due to post-transplant lymphoproliferative disease (PTLD), a few months later tacrolimus replaced MPS because of gastrointestinal symptoms. To increase adherence, a prolonged-release tacrolimus formulation was introduced 8 years after KTx. Because of ongoing nonadherence, belatacept replaced tacrolimus 12 years after KT.

Patient 3 received cyclosporine A and everolimus for maintenance immunosuppression but experienced a steep decline in GFR due to marked nonadherence which resulted in acute humoral rejection or episodes of dehydration. Belatacept was introduced to replace cyclosporine A at a state of severely impaired chronic transplant dysfunction.

Patient 4 was treated with belatacept from week 12 after KTx because of nonadherence. Initial immunosuppression consisted of basiliximab on days 0 and 4, prednisolone and cyclosporine A; everolimus was added per protocol after 4 weeks. The course up to switching from cyclosporine A to belatacept was complicated by an infected hematoma after laparoscopic nephrectomy, interstitial pneumonia, postrenal acute kidney injury due to blood clots after removal of a ureteral stent, toxic severe aplastic anemia and combined cellular and humoral rejection treated with prednisolone pulses, immunoglobulins and rituximab. After the rejection was diagnosed, the patient and his parents acknowledged nonadherence.

Patient 5 was treated with belatacept in addition to MMF and prednisolone from week 11 after second KTx as a replacement for cyclosporine A. Reason for initiation of belatacept therapy was an acute cellular rejection classified as Banff IIa (treated initially with prednisolone pulses and then with antithymocyte globulin 3 months after start of belatacept because of ongoing loss of graft function) due to nonadherence to the previous immunosuppressive regimen. In this patient, nonadherence was the cause of the loss of the first graft and it was also observed before transplantation under hemodialysis. Therefore, retransplantation was retarded until after psychological interventions, it was concluded that the patient would be adherent enough for a second transplantation. Unfortunately,

the same behavioral patterns re-established after second transplantation. Two months after starting belatacept, significant neutropenia was observed which required treatment with filgrastim. At that time point, the area under the curve concentration of mycophenolic acid was 78 mg × h/l. Because of the neutropenia, MMF was switched to everolimus and leukocyte counts eventually normalized.

Patient 6 was switched from cyclosporine A to belatacept after a combined cellular and humoral rejection classified as Banff 2/II and 4/IA due to nonadherence 12 months after KTx. Additional treatment of rejection included prednisolone pulses, plasmapheresis, rituximab, immunoglobulins, antithymocyte globulin and bortezomib.

Treatment efficacy

In Patient 1, who received belatacept 23 days after transplantation, eGFR increased in the first months after KTx as is commonly seen in uncomplicated courses (Fig. 1). Patients 4 and 5 were treated early with belatacept, both because of proven acute rejection due to nonadherence; after initiation of treatment with belatacept, renal function stabilized and slightly improved. In Patient 5, however, additional treatment with antithymocyte globulin was necessary for controlling rejection after the start of belatacept.

Patient 2 received belatacept to ensure effective immunosuppression after many years of nonadherence and this led to stabilization of eGFR. In Patient 3, belatacept was started at a markedly impaired eGFR and led to a change in slope of eGFR, thus delaying initiation of hemodialysis. In Patient 6, belatacept was also started at a point of markedly impaired eGFR and after a steep decline in renal function in the previous months; the long-term effect of belatacept in this patient has still to be determined.

Adverse effects

Clinically relevant neutropenia was observed in Patient 5. As this is a known adverse effect of both belatacept and the concurrently used MMF, it is not possible to determine which agent was implicated, although as there was improvement after its cessation MMF appears the more probable of the two. No other adverse effects were documented.

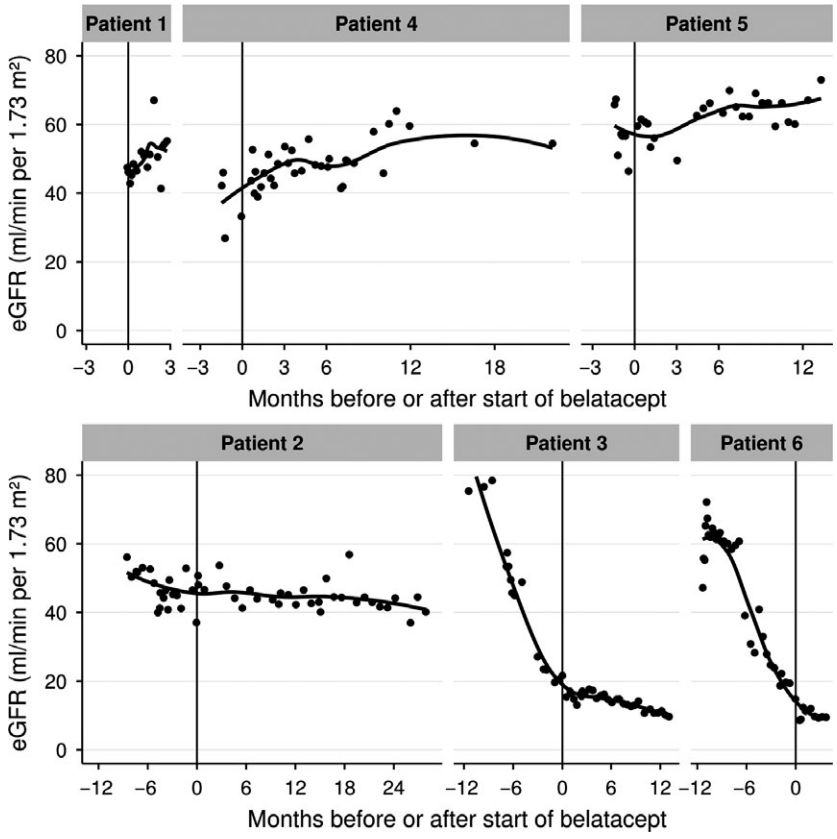

Figure 1 Course of estimated glomerular filtration rate (eGFR) before and after start of treatment with belatacept. Vertical line denotes start of belatacept therapy. The upper row depicts patients who received belatacept early; the lower row depicts patients who received belatacept late after kidney transplantation (KTx).

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Adherence

Despite a demanding treatment schedule with four intravenous infusions during the first month of treatment and 4-weekly infusions thereafter, adherence to this component of immunosuppression was complete in all six patients, that is 100% of patients kept all outpatient appointments for administration of belatacept in our outpatient clinic. All patients and families who were offered treatment with belatacept agreed to continuous intravenous infusions and did not refuse this new option.

Case description of patients for safety assessment

Patient 7 received belatacept in combination with prednisolone, low-dose cyclosporine A and everolimus because of recurrence of focal segmental glomerulosclerosis (FSGS), the primary disease, in the second KTx with the idea that by blocking B7-1, FSGS relapse could be treated [8]. Belatacept was started 14 months after the second KTx at the age of 13 years and continued for 22 months until initiation of hemodialysis. There were no apparent adverse drugs events and adherence to belatacept treatment was complete.

Patient 8 received a KTx when 14 years old. The initial immunosuppression was basiliximab for induction, prednisolone and a combination of low-dose cyclosporine A and everolimus as maintenance immunosuppression. Two and a half years after transplantation, cyclosporine A was switched to tacrolimus because of humoral rejection. This worsened preexisting type 1 diabetes mellitus, and at the age of 17, the patient was therefore switched from tacrolimus to belatacept, leading to better controlled diabetes mellitus. Four months after the beginning of treatment with belatacept, GFR was stable at 48 ml/min per 1.73 m^2 and there have been no apparent adverse drug events. No belatacept treatments were missed. After transfer to an adult nephrologist, belatacept treatment is ongoing.

Discussion

This is the first study on the use of belatacept after KTx in adolescents with severe nonadherence to twice-daily oral ingestion of classical immunosuppressants. We observed complete adherence to belatacept despite the inconvenient intravenous application every 4 weeks in the maintenance phase. Indeed, some patients revealed a strong preference for the new treatment option. They accepted the intravenous schedule, understanding that it would secure long-term graft function and help them to overcome the problem of adherence.

We observed a lesser slope of the GFR loss for those patients switched to belatacept at a relatively late stage post-transplantation as well as an improving graft function for those on an early switch.

After a cumulative treatment duration of 83 months in six patients, we observed one acute rejection. Considering two additional patients who received belatacept for other reasons, the cumulative treatment duration for safety was 109 months; the single observed adverse event of severe neutropenia ceased after discontinuation of MMF.

Belatacept is approved for combination therapy with MMF, an antiproliferative agent. Most of our patients received a mammalian target of rapamycin (mTOR) inhibitor (everolimus or sirolimus) in combination with belatacept because the combination of a CNI and an mTOR inhibitor was in place before the switch from CNI to belatacept. In support of this, an exploratory randomized trial showed better eGFR after 1 year under belatacept and MMF or belatacept and sirolimus compared to tacrolimus and MMF, with acceptable rates of acute rejection [9]. Considering other potential drugs for combination therapy with belatacept, it has to be noted that CNIs appear to antagonize the effects of costimulatory blockade [10]. Thus, a combination therapy of belatacept with tacrolimus or cyclosporine is not recommended due to this mechanism which would also counteract the aim of an immunosuppressive regimen without CNIs.

Seronegativity for Epstein–Barr virus (EBV) or unknown EBV status are explicit contraindications for the use of belatacept because of the increased risk of EBV-negative patients to develop PTLD during treatment with belatacept. This is a potential obstacle in younger patients, because data from the USA show that only 54% of children between 6 and 8 years are seropositive for EBV compared to 83% of people aged 18 or 19 years [11]; thus, the requirement of EBV seropositivity excludes a significant proportion of children and adolescents which therefore limits the use of belatacept in minors. In our cohort, all patients showed seropositivity for EBV immediately before the start of belatacept. In one patient, however, the seropositivity was only transient, maybe due to previous treatment with immunoglobulins; reassuringly, after 22 months, there are no signs of PTLD in this patient.

In the three patients who received belatacept early after KTx, an increase in GFR could be observed. Interestingly, this effect is independent of a proposed remaining nonadherence with the second oral immunosuppressant (MMF or everolimus) which patients were advised to take in combination with belatacept.

Consequently, it might be speculated, that belatacept therapy alone or at least with a not consequent combined administration of antiproliferative drugs might be sufficient for reaching an adequate grade of immunosuppression protecting from rejection. In a very selected population, 7 of 20 adult recipients of a first live donor kidney allograft could be weaned from any oral immunosuppressant making belatacept the single immunosuppressive agents [12]. In addition, a clinical trial studying withdrawal of steroids and antiproliferatives in adult kidney transplant recipients after 7 years of combination therapy with belatacept is registered (ClinicalTrials.gov Identifier: NCT02939365). However, further evidence is needed for belatacept monotherapy.

Switching to belatacept has been shown to increase GFR, in general regardless of time after KTx or of GFR at the beginning of belatacept treatment [13–15]. These positive effects of belatacept on graft function, even on patients with normal adherence, can obviously also be expected in adolescents with nonadherence to oral immunosuppressive therapy. Therefore, belatacept-based immunosuppression in adolescents with nonadherence to classical oral immunosuppressive drugs seems to be a viable option. Of particular interest is the lack of any barrier to adherence of the substantially longer time required for belatacept infusion during scheduled outpatient appointments compared to standard appointments.

Using an intravenous therapy instead of oral administration of immunosuppressants is associated with the issue of repeated intravenous cannulations with its attending vascular insult and possible compromise of future vascular access for hemodialysis. As kidney graft recipients are at high risk for return to hemodialysis after graft failure, this point has to be valued within the decision process of switching of immunosuppressive therapy in nonadherent adolescents.

With regard to the future, there are several interesting trials currently under way, firstly, for example, belatacept compared to tacrolimus (ClinicalTrials.gov Identifier: NCT02152345). The major trials have been criticized for choosing cyclosporine as the comparative treatment and not the supposedly superior quasi-gold standard tacrolimus; this investigator-initiated trial could address this criticism. Second, the question as to whether the treatment schedule of belatacept could be extended to 8 weeks is also under investigation (ClinicalTrials.gov identifier: NCT02560558 and NCT02939365). Lastly, newer costimulation blockers have been developed and await further drug development studies [16,17]. A single-dose study of belatacept in adolescents with stable kidney graft function is ongoing (ClinicalTrials.gov identifier: NCT01791491). The manufacturer of belatacept, Bristol–Myers Squibb, has announced a CNI-to-belatacept conversion trial in adolescents, with enrollment from early 2018 (BMS, personal communication).

Conclusion

Results of ongoing and planned trials on the use of belatacept therapy in adolescents will still have to be awaited before drawing final conclusions for the routine use of belatacept in adolescent kidney recipients. In the meantime, conversion to belatacept-based immunosuppression can be considered as an option for nonadherent, EBV-seropositive, adolescent kidney transplant recipients if administered early enough before deterioration of graft function.

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Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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